REMARKS

Rejections of Claims and Traversal Thereof

In the June 3, 2005 Office Action,

claims 1-3, 6-11, 13-16, 24 and 73-79 were rejected U.S.C. §112, first paragraph as failing to comply with the written description requirement. This rejection is hereby traversed because there is no infirmity in the presently claimed invention under §112, first paragraph, written description requirements.

Claim 1 is representative of applicants' claimed invention and recites as follows:

> 1.A chimeric polypeptide comprising:
>
> > a virus coat polypeptide sequence, a viral cell surface receptor polypeptide and an amino acid sequence spacer , wherein the amino acid sequence of the chimeric polypeptide is a full length reference sequence, a truncated sequence or a modified sequence, wherein the modified sequence has about 95% identity to the full length reference or truncated sequence and has the functionality of forming an intramolecular interacting complex between the virus coat polypeptide and viral cell surface receptor, wherein the virus is an immunodeficiency virus selected from the group consisting of retroviruses HIV, SIV, FIV, and FeLV, wherein the viral cell surface receptor polypeptide sequence comprises amino acid residues of the region of CD4 having binding affinity for the virus coat polypeptide sequence, and the amino acid sequence spacer is linked to both the virus coat polypeptide sequence and the viral cell surface receptor polypeptide sequence and positioned therebetween to form a single chain polypeptide of peptidic bonds, wherein the spacer consists of an amino acid sequence of sufficient length to allow the single chain polypeptide to fold thereby permitting the virus coat polypeptide sequence and the viral cell surface receptor polypeptide sequence to form -the intramolecular interacting complex.

Applicants' invention is directed to a chimeric polypeptide that comprises polypeptides from a ligand-receptor pair that have a binding affinity for each other. One of ordinary skill in the art

reading the instant specification would be compelled by such disclosure to the conclusion that applicants fully possessed the invention at the time of filing. The Office's contrary assertion that "neither the viral coat nor the viral receptor have not been sufficiently described in terms of their structure and function" is simply at fundamental odds with the clear and unambiguous disclosure of the specification.

The Federal Circuit has addressed the written description requirement, (See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002)) and adopted the standard that

> "the written description requirement can be met by 'showing that an invention is complete by disclosure of **sufficiently detailed, relevant identifying characteristics** . . . i.e., **complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.**'" (Emphasis added) Id. at 1613 .

The court in *Enzo* adopted its standard from the USPTO's Written Description Examination Guidelines. See, 63 USPQ2d at 1613 (citing the Guidelines).

Applicants note that the Federal Circuit **clearly stated** that written description requirements are met when functional characteristics are coupled with a **known** or disclosed correlation between function and structure. Importantly, the standards of the *Enzo* Court were recently reiterated and clarified by the Federal Circuit in *Capon v. Eshhar*, Fed. Cir., No. 03-1480, on August 12, 2005. Specifically, the *Capon* Court stated that the law must take cognizance of the scientific facts and the state of scientific knowledge at the time of filing. More specifically, Judge Newman explained as follows:

> "The 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution."

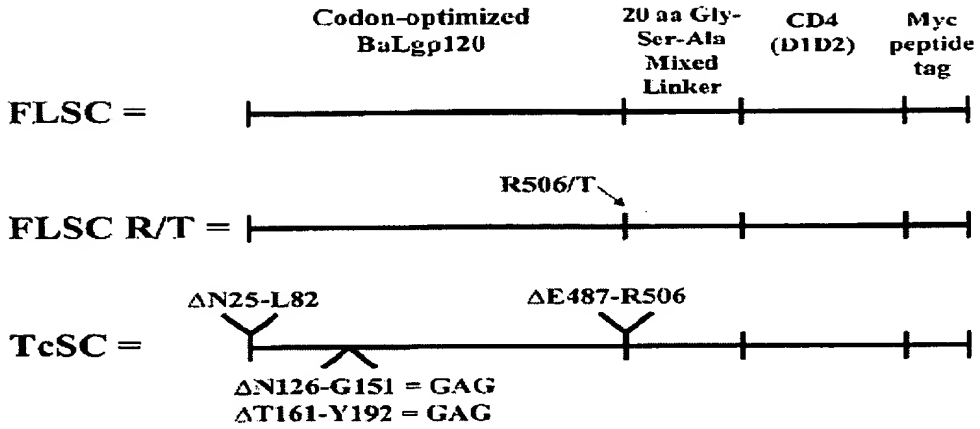
Thus, the *Capon* Court ruled that known information does not necessary have to be reiterated in the disclosure. Interestingly, the Capon matter is similar to applicants presently claimed invention. The chimeric polypeptides of present invention include full length virus coat polypeptides and surface cell receptor CD4 polypeptides having known structure and function.

The function and structure of the viral coat polypeptides for HIV, SIV FIV and FeLV have been known since at least the early 1990s. Likewise, the function and structure of CD4 has been known as long. Further, the interaction and binding affinity of the coat polypeptide for the CD4 receptor has been known. Numerous researchers, in the late 1980s, recognized the specificity of the viral envelope glycoprotein gp120 for CD4 receptors on T cells. For example, the Berger group in 1988[1] discussed the interaction of CD4 and the envelope protein gp120. Further, it was known that infection with SIV included gp120 binding to CD4 thereby leading to conformational changes and virus-cell membrane fusion. (See Doms, et al. (1990))[2] Information relating to FIV (feline immunodeficiency virus) and FeLV (feline leukemia virus) exhibit similar mechanisms and effects, such as a depletion of CD4 T cells during the course of the infection.[3] The references discussed herein are included in Appendix A.

Notably, nucleotide sequences encoding these discussed polypeptides have been available since the early 1990s and can be easily obtained from NCBI.

Thus, according to the *Enzo* and *Capon* Courts, information already known does not have to be disclosed in the specification to meet the "written description" requirements. However, applicants have clearly provided such information in the disclosure especially relating to HIV coat polypeptides, full length, truncated or modified chimeric polypeptides relating to HIV. For example, Figure 1, recreated below for ease of discussion, provides guidance for the structure of the FLSC, FLSC with a substitution at a specific amino acid residue, and the truncated single chain polypeptide.

[1] Berger, et al., Proc. Natl. Acad. Sci USA, V 85, pp. 2357-2361.
[2] Doms, et al., Journal of Virology, V. 64(7), pp 3537-3540.
[3] Ackley, et al. (1990) Journal of Virology V. 64(11), pp 5652-5655.



Further, the examples set forth in the disclosure provide more than ample information showing that applicants were in possession of the invention at the time of filing. The chimeric single chain polypeptides of the present invention are novel and non-obvious and the function and related structure are clearly described in the examples.

Example I describes the construction of a polynucleotide encoding a single chain gp120-CD4 chimeric polypeptide FLSC, modified FLSC-R/T and truncated version. A single chain nucleic acid encoding a gp120-CD4 chimeric polypeptide was constructed by arranging the respective coding sequences in the following order: (1) at the 5' end, a synthetic, codon encoding gp120 of the macrophage-tropic HIVs, BaL; (2) a sequence encoding a 20 amino acid linker consisting of glycines, alanine, and serines; (3) sequences for soluble CD4 domains 1 and 2 (DlD2); and (4) at the 3' end, sequences encoding a short polypeptide derived from the c-myc oncogene for FLSC. FLSC-R/T included a mutation at the c-terminal end of gp102 to replace a threonine with an arginine. The codon optimized gpl20 sequence was used as it permits high-level expression in a rev-independent manner (Haas, J., *et al., Curr. Biol., 6:3 15-24 (1996)).* The human CD4 sequence used was derived from T4-pMV7 (Maddon, P. J., et *al., Cell,* 47:333-48 (1986); NIH AIDS Reagent Repository, Bethesda, MD). The myc polypeptide sequence allows convenient analyses, purification, and other manipulation of the chimeric polypeptide. There is a full discussion relating to the construction of such chimeric polypeptides at page 40 of the specification.

Thus, the present invention provides ample written description for the production of the chimeras of the present invention.

Example II provides instruction for transfecting cells with nucleotide sequences that encode for the chimeric polypeptides and further provides for the advantages of mutation of the furin cleavage site.

Example IV describes the data demonstrating the binding of gpl20-CD4 chimeric molecules, containing a CCR5-specific HIV envelope sequence, to CCR5 expressing cells. **Interestingly the results shown in this example demonstrate the binding affinity of gp120 with CD4 whether in full length or truncated form.** The formation of the gp120-CD4 complex normally exposes the envelope domains that interact with an appropriate co-receptor (M. Thali *et al., J Virol.,* 67:3978-86 (1993); M.A. Vodicka *et al., Virol.,* 233: 193-8 (1997)). Therefore, another measure of properly folded gp120-CD4 complexes and its ability to inhibit virus infection of a cell is the ability to bind to a CCR5 co-receptor.

To evaluate the ability of the single-chain complexes to bind co-receptor, purified single-chain gp120-CD4 molecules were allowed to interact with cells that express either CCR5 or CXCR4. As shown in FIG. 6, both single chain gp120-CD4 complexes (FLSC and TcSC) bound to the CCR5-expressing, but not CXCR4-expressing, L1.2 cells. As stated by applicants, at page 47, the absence of binding to CXCR4 in these studies was not entirely unexpected in view of the apparent specificity of the HIV envelope polypeptide in the gpl20-CD4 chimera for CD4. Interestingly, applicants further provide guidance that modifying a virus coat polypeptide, as described herein, it is possible to obtain a chimeric polypeptide that binds to another co-receptor.

Example V, at page 48 of the application, describes data demonstrating that a gp120-CD4 chimeric molecule can neutralize infection by HIV strains using the same co-receptor. As shown in FIG. 8, both FLSC and TcSC potently and selectively neutralized the R5 HIV-l BaL isolate, while there was only a slight inhibition (ID_{90} > 10 ug/ml) of 2044 isolate. Thus, the data demonstrate that a virus coat polypeptide-receptor chimeric molecule can bind to a cellular co-receptor thereby blocking binding or infection of the cells by virus that utilize the co-receptor for binding or infection.

Example VI further describes the construction and expression of a modified gpl20-CD4 chimeric polypeptide having an immunoglobulin polypeptide sequence, gpl20-CD4-IgGl. This exemplary heterologous domain adds functionality to the gpl20-CD4 chimeric polypeptide, including adhesin and immunopotentiating functions, prolonging stability, increasing circulating half-life and ability to cross the placental barrier. This example also shows that the gp120-CD4-IgG1 chimera binds to co-receptor expressed on the surface of intact cells and neutralizes HIV virus. This interaction permits the infection of HIV-1 into target CD4+ cells. Antibodies or other agents that interfere with the interaction of HIV-l with the co- receptor can prevent infection.

Instructions are provided in the specification for preparing and determining the activity of the chimeras having an additional heterologous domain. As shown in FIG. 11, gp120-CD4-IgGl binds specifically to L 1.2 cells that express CCR5. These studies indicate that heterologous domains conferring additional or enhanced functionality can be added to chimeric molecules without affecting their ability to form a complex that binds to cell co-receptor.

Further applicants showed that gp120-CD4-IgGl was just as effective as known antibodies in blocking virus entry into cells, as shown below in Table 2 recreated from the application.

TABLE 2

Neutralization of X4, R5, and X4/R5 HIV by FLSC-IgG1

U373/CD4/CCR5					
	FLSC-IgG1	2G12	2F5	IgG1b12	Control IgG
	ID90 (μg/mL)				
BaL	3.1	>10	>10	1.57	>10
ADA	4.58	>10	>10	>10	>10
89.6	3.56	8.07	>10	3.39	>10

U373/CD4/CXCR4					
	SCIg	2G12	2F5	IgG1b12	Control IgG
	ID90 (μg/mL)				
2044	>10	>10	>10	1.57	>10
2005	>10	>10	>10	>10	>10
89.6	>10	>10	>10	5.34	>10

The data in Table 2 indicate that FLSC-IgG blocks viruses that use R5 for cell entry. FLSC-IgG neutralizes virus as effective as 2G12, 2F5, and IgG1b12, antibodies that are currently being evaluated in passive immunotherapy trials. These data therefore further affirm the usefulness of gp120-CD4 chimeras to inhibit HIV infection in particular, and the applicability of virus coat protein-receptor chimeras as inhibitors of other viruses that utilize co-receptor for binding or cell penetration in general.

Thus, the present application describes the claimed subject matter and one skilled in the art would have no difficulty in discerning that applicants were in possession of all aspects of the claimed invention at the time of filing.

According to the Office:

> "Claiming a product based on function (i.e. that the viral coat protein and the receptor protein are capable or interacting) does not provide sufficient description of the product as claimed. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities."

The Office provides numerous references that discuss the uncertainty involved in a substitution or deletion in the amino acid sequence. However, applicants have amended the claims herein to conform with instructional guidance set forth in the "Written Description" Training Manual, and as such, the multiplicity of references provided by the Office are no longer relevant.

Applicants reviewed the training material entitled "SYNOPSIS OF APPLICATION OF WRITTEN DESCRIPTION GUIDELINES" and submit that all pending claims meet the requirements describes in this training material. Specifically, applicants reviewed Example 14 because this example describes a product by function that is closest to the presently claimed invention, as indicated by the Office in the previous statement. Using the analysis set forth in the guidelines, applicants submit that the presently claimed invention fully meets the written description requirements.

For example, a review of the full content of the specification indicates that the chimeric polypeptides includes sequences for a virus coat polypeptide and cell surface receptor having amino acid sequences known to the skilled artisan. The chimeric polypeptide of the present invention are novel and unobvious and have the function of forming an intramolecular interactive binding complex. The procedures for making the variant or modified sequences are conventional and an assay is described in the specification that will identify chimeric variants that have the same functional ability of forming the intramolecular interactive binding complex.

Applicants have defined a modified sequence in the specification as polypeptides that will retain activity or function associated with unmodified chimeric polypeptide. Modified chimeric polypeptides will generally have an amino acid sequence "substantially identical" or "substantially homologous" with the amino acid sequence of the unmodified polypeptide. The term "substantially identical" or "substantially homologous," was defined in the specification as a sequence of the polypeptide is at least 50% identical to a reference sequence. Modified polypeptides and substantially identical polypeptides will typically have at least 70%, alternatively 85%, more likely 90%, and most likely 95% homology to a reference polypeptide. Further it is stated in the specification that substantially identical or homologous polypeptides include additions, truncations, internal deletions or insertions, conservative and non-conservative substitutions, or other modifications located at positions of the amino acid sequence which do not destroy the function of the chimeric polypeptide (as determined by functional assays, e.g., as described herein). Substantially identical or homologous polypeptides also include those having modifications that improve or confer an additional function or activity. For example, FLSC R/T has a mutated furin site which increases stability of the modified FLSC (see, e.g., FIG. 13).

Since the chimeric product is novel and unobvious and there is actual reduction to practice of the full length, truncated and modified chimeric (FLSC R/T) then the numerous species have been disclosed. Further, as stated in the guidelines, because there is an assay disclosed by applicants which will provide a method for identifying the functionality of all variants having at least 95% identity, one skilled in the art would conclude that applicants were in possession of the necessary common attributes possessed by the members of the genus.

As stated above, Example IV describes an assay that determines and shows the interaction between viral coat polypeptide and the cell surface receptor to form the intramolecular complex. The formation of the gp120-CD4 complex normally exposes the envelope domains that interact with an appropriate co-receptor (M. Thali *et al., J Virol.,* 67:3978-86 (1993); M.A. Vodicka *et al., Virol.,* 233: 193-8 (1997)). Therefore, an appropriate measure of properly folded gp120-CD4 complexes and its ability to inhibit virus infection of a cell is the ability to bind to a CCR5 co-receptor.

The specification provides a clear and concise method to evaluate the ability of the single-chain complexes to bind co-receptor wherein purified single-chain gp120-CD4 molecules were allowed to interact with cells that express either CCR5 or CXCR4. For the binding, the purified single-chain preparation was allowed to interact with L1.2 cells that express CCR5 (L. Wu et al., *Nature,* 384: 179-I 83 (1996); L. Wu *et al., J. Exp. Med.,* 186: 1373-8 1 (1997)). L1.2, L1.2/X4, and L 1.2/R5 cells, murine B-cells lines that express no co-receptor, CXCR4, or CCR5 were mixed with decreasing concentrations of purified single-chain protein. After incubation at 37°C for 1 hour, the cells were washed. Bound single-chain molecules were detected with 1 ug/ml of Mab C11 (J.E. Robinson et *al., J Cell. Biochem. Suppl.,* 16E:71 (1992); M. Thali *et al., J Virol.,* 67:3978-86 (1993), an anti-gp 120 Mab, followed by an anti-human IgG that was labeled with a fluorescent molecule, phycoerythrin. C11 recognizes a conformational determinant formed by the C 1 -C4 regions. The level of bound fluorescence was determined by fluorescence activated cell sorting (FACS) analysis with a FACS Calibur instrument (Beckton Dickinson). The mean fluorescence intensity for each sample was calculated using the Cell Quest 3.1.3 program (Beckton Dickinson).

As shown in FIG. 6, both single chain gp120-CD4 complexes (FLSC and TcSC) bound to the CCR5-expressing, but not CXCR4-expressing, L1.2 cells. Maximal binding was observed with FLSC at concentrations (10 *ug*/ml) equivalent to what was observed with soluble BaL gp120-rsCD4 complexes tested as controls. In comparison, approximately 10-fold higher concentrations of the TcSC were required to approach saturation binding. Thus, gp120-CD4 chimeric polypeptide presents functional co-receptor binding site(s) for CCR5, as expected for a molecule containing a macrophage tropic gp120. In sum, the data demonstrate the successful expression of a soluble, chimeric polypeptide which duplicates the transition state conformation of a virus coat-receptor complex.

Thus, applicants submit, in light of the analysis set forth in the PTO guidelines, which applicants should be able to depend on for guidance, the disclosure meets the requirements of 35 U.S.C. §112, first paragraph and provides adequate written description for the claimed invention.

According to the Office:

> "The mere contemplation of the claimed genus in the specification is not sufficient to support the presently claimed invention directed to a genus of polypeptide including the viral coat and viral receptor chimera that may interact. . . . Claiming a genus of polypeptide sequences that must posses the biological properties as contemplated by applicants' disclosure without defining what means will do so is not in compliance with the written description requirement."

Thus, the Office seem to be believe that the specification does not adequately support the breadth of all of the claims insofar as one cannot know the effectiveness of all the permutations and combinations covered by the claims. Interestingly, the *Capon* Court also address this very issue and ruled that "It is not necessary that every permutation within a generally operable invention be effective for an inventor to obtain a generic claim as long as the effect is sufficiently demonstrated to characterize a generic invention." The Court further stated that "predictability or unpredictability of the science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention. Our predecessor court summarized in *In re Storrs*, 245 F.2d 474, 478 (CCPA 1957) that "[i]t must be borne in mind that, while it is necessary that an applicant for a patent give to the public a complete and adequate disclosure in

return for the patent grant, the certainty required of the disclosure is not greater than that which is reasonable, having due regard to the subject matter involved."

Clearly, the results set forth in the examples included in the specification, in light of that known to one skilled in the art, provide information that the retroviruses covered within the scope of the claims exhibit a binding affinity between the virus coat polypeptide and cell surface receptor polypeptide and are sufficient to demonstrated a generic invention.

Applicants submit that the Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker,* 24 USPQ2d 1443 (Fed. Cir. 1992). Insofar as the written description requirement is concerned, that burden is discharged by "presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined in the claims." *In re Wetheim,* 191 USPQ 90, (C.C.P.A. 1976). In the present situation, the specification contains a description of the claimed invention, as shown above, and thus the Office, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient. *In re Alton,* 37 USPQ2d 1578 (Fed. Cir. 1996). The Office has not met this burden.

Thus, applicants submit, in light of the analysis set forth in the PTO guidelines, that the disclosure meets the requirements of 35 U.S.C. §112, first paragraph and provides adequate written description for the claimed invention. Applicants respectfully request the withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

Rejoinder of Method Claims

When an application as originally filed discloses a product and the process for making and/or using such product, and only the claims directed to the product are presented for examination, when a product claim is found allowable, applicant may present claims directed to the process of making and/or using the patentable product for examination through rejoinder procedure in accordance with MPEP §821.04, provided that the process claims depend from or include all the limitations of the allowed product claims.

The currently pending method claims include all the limitations of the product claims and meet all standards of enablement, written description and definiteness under 35 U.S.C. §112. Accordingly, the method claims are in form suitable for future examination upon their rejoinder with the allowed product elected claims. Applicants are requesting that all method claims be rejoined, examined and found allowable.

Fee Payable and Petition for One-Month Extension

Applicants hereby petition for a one-month extension of time, extending the deadline for responding to the June 3, 2005 Office Action from September 3, 2005 to October 3, 2005. The entry of this petition results in a petition fee of $60.00. A credit card form in the amount of $60.00 is submitted herewith. Authorization is hereby given to charge any deficiency in applicable fees for this response to Deposit Account Number 08-3284 of Intellectual Property/Technology Law.

Conclusion

Applicants have satisfied all the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Winkler reconsider the patentability of pending claims in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Winkler is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

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APPENDIX A